

**Title 20—DEPARTMENT OF INSURANCE, FINANCIAL INSTITUTIONS AND
PROFESSIONAL REGISTRATION
Division 2220—State Board of Pharmacy
Chapter 2—General Rules**

PROPOSED AMENDMENT

20 CSR 2220-2.200 Sterile *[Pharmaceuticals]* Compounding. The board is amending the title, purpose statement, and all sections of this rule. Additionally, the board is deleting sections (5), (6), (8), (15), and (16) of the current rule and adding new sections (5), (6), (7), (10), (17), (18), (20), and (21).

PURPOSE: This board is amending all sections of this rule to update, clarify, and delineate requirements for sterile compounding pharmacies.

*PURPOSE: This rule establishes standards for the *[preparation]* **handling**, labeling *[and]*, distribution, **and dispensing** of *[sterile pharmaceuticals]* **compounded sterile preparations** by licensed pharmacies, pursuant to a physician's order or prescription.*

(1) Definitions.

- (B) Batch: Compounding of multiple sterile *[product]* **preparation** units in a single discrete process, by the same individuals, carried out during one (1) limited time period.
- (D) Biological safety cabinet: Containment unit suitable for the preparation of low to moderate risk agents where there is a need for protection of the *[product]* **preparation**, personnel and environment, according to National Sanitation Foundation (NSF) International standards.
- [(E) Class 100 environment: an atmospheric environment which contains less than one hundred (100) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.*
- (F) Class 10,000 environment: An atmospheric environment which contains less than ten thousand (10,000) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.*
- (G) Clean room: A room—
 - 1. In which the concentration of airborne particles is controlled;*
 - 2. That is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room; and*
 - 3. In which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.*
- (H) Clean zone: Dedicated space—
 - 1. In which the concentration of airborne particles is controlled;*
 - 2. That is constructed and used in a manner that minimizes the introduction, generation, and retention of particles inside the zone; and*
 - 3. In which other relevant variables (e.g., temperature, humidity, and pressure)*

are controlled as necessary.

This zone may be open or enclosed and may or may not be located within a clean room.]

- (E) Buffer Area:** An ISO Class 7 or better area where the primary engineering control is physically located that is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room and in which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

[(I)](F) Compounding: For the purposes of this regulation, compounding is defined as in 20 CSR 2220-2.400(1). Compounded sterile medications may include, but are not limited to[, *injectables, parenteral nutrition solutions, irrigation solutions, inhalation solutions, intravenous solutions and ophthalmic preparations.*]:

1. **Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals** that must or are required to be sterile when they are administered to patients, including, but not limited to the following dosage forms: bronchial and inhaled nasal preparations intended for deposition in the lung, baths and soaks for live organs and tissues, epidural and intrathecal solutions, bladder/wound solutions, injectables, implantable devices and dosage forms, inhalation solutions, intravenous solutions, irrigation solutions, ophthalmic preparations, parenteral nutrition solutions, and repackaged sterile preparations. Nasal sprays and irrigations intended for deposit in the nasal passages may be prepared as nonsterile compounds;
2. An FDA approved manufactured sterile product that is either prepared according to the manufacturers' approved labeling/recommendations or prepared differently than published in such labeling; and
3. Assembling point-of-care assembled systems.

(G) Compounding Aseptic Containment Isolator (CACI): A restricted access barrier system (RABS) that is designed for compounding sterile hazardous drugs and designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment for CSPs.

(H) Compounding Aseptic Isolator (CAI): A RABS specifically designed for compounding sterile non-hazardous pharmaceutical ingredients or CSPs and designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes.

[(J)] Controlled area: For purposes of these regulations, a controlled area is the area designated for preparing sterile products preparations or an area designated for preparing sterile preparations that is separated from other activities/operations by a line of demarcation that clearly separates the area from other operations. This is referred to as the buffer zone (i.e., the clean room in which the laminar airflow workbench is located) by the United States Pharmacopoeia (USP).]

(I) Controlled area: For purposes of these regulations, a controlled area is a separate room designated for preparing sterile preparations or an area designated for preparing sterile preparations that is separated from other activities/operations by a

line of demarcation that clearly separates the area from other operations.

[(K)](J) Critical area: Any area in the controlled area where **[products] preparations** or containers are exposed to the environment.

[(L)] (K) Critical site: *[An opening providing a direct pathway between a sterile product and the environment or any surface coming into contact with the product or environment.] Any surface, pathway or opening (e.g., vial septa, injection ports, beakers, needle hubs) that provides a direct pathway between a compounded sterile preparation or other ingredient used to compound a sterile preparation and the air, environment or moisture or that poses a risk of touch contamination.*

(L) CSP: Compounded sterile preparation.

[(M)] Critical surface: *Any surface that comes into contact with previously sterilized [products] or containers.]*

[(N)](M) Cytotoxic drugs: A pharmaceutical product that has the capability of direct toxic action on living tissue that can result in severe leukopenia and thrombocytopenia, depression of the immune system and the alteration of a host's inflammatory response system.

[(O)](N) Emergency dispensing: Is a situation where a Risk Level 3 **[product] preparation** is necessary for immediate administration of the **[product] preparation** and no alternative product **or preparation** is available and the prescriber is informed that the **[product] preparation** is being dispensed prior to appropriate testing. Documentation of the dispensing of the **[product] preparation**, the prescriber's approval for dispensing prior to the receipt of test results and the need for the emergency must appear within the prescription record. A separate authorization from the prescriber is required for each emergency dispensing.

[(P)](O) High-Efficiency Particulate Air (HEPA) filter: A filter composed of pleats of filter medium separated by rigid sheets of corrugated paper or aluminum foil that direct the flow of air forced through the filter in a uniform parallel flow. HEPA filters remove ninety-nine point ninety-seven percent (99.97%) of all particles three-tenths (0.3) microns or larger. When HEPA filters are used as a component of a horizontal- or vertical-laminar-airflow workbench, an environment can be created consistent with standards for a **[Class 100 clean room] ISO Class 5 environment**.

(P) In-Use Time/Date: The time/date before which a conventionally manufactured product or a CSP must be used after it has been opened or needle-punctured.

[(Q)] Isolator (or barrier isolator): *A closed system made up of four (4) solid walls, an air-handling system, and transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with coving between wall junctures. The air-handling system provides HEPA filtration of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half suits.]*

(Q) ISO Class 5: An area with less than three thousand five hundred twenty (3,520) particles (0.5 µm and larger in size) per cubic meter.

(R) ISO Class 7: An area with less than three hundred fifty-two thousand (352,000) particles (0.5 µm and larger in size) per cubic meter.

(S) Multiple-Dose Container: A multiple unit container for articles or compounded sterile preparations that contains more than one (1) dose of medication and usually contains an antimicrobial preservative.

[(R)](T) Parenteral: A sterile preparation of drugs for injection through one (1) or more layers of skin.

(U) Point of Care Assembled System: A closed system device that creates a physical barrier between diluents, fluids, or other drug components and is designed to be activated by the end user by allowing the components to mix prior to administration.

(V) Primary Engineering Control (PEC): A system that provides an ISO 5 environment for the exposure of critical sites when compounding sterile preparations. PECs include, but may not be limited to, horizontal/vertical laminar airflow hoods, biological safety cabinets, RABS such as compounding aseptic isolators (CAIs) or compounding aseptic containment isolators (CACIs).

[(S)](W) Process validation or simulation: Microbiological simulation of an aseptic process with growth medium processed in a manner similar to the processing of the *[product] preparation* and with the same container or closure system.

[(T)](X) Quality assurance: For purposes of these regulations, quality assurance is the set of activities used to ensure that the processes used in the preparation of sterile drug *[products] preparations* lead to *[products] preparations* that meet predetermined standards of quality.

[(U)](Y) Quality control: For the purposes of these regulations, quality control is the set of testing activities used to determine that the ingredients, components and final sterile *[products] preparations* prepared meet predetermined requirements with respect to identity, purity, nonpyrogenicity and sterility.

(Z) Restricted access barrier system (RABS): A primary engineering control that is comprised of a closed system made up of four (4) solid walls, an air-handling system, and transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with coving between wall junctures. The air-handling system provides HEPA filtration of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half suits. Examples of a RABS may include, but is not limited to, a CAI or CACI.

[(V)](AA) Repackaging: The subdivision or transfer of a compounded *[product] preparation* from one container or device to a different container or device.

[(W)] *Sterile pharmaceutical: A dosage form free from living microorganisms.*

(BB) Single-Dose/Single-Unit Container/Vial: A container/vial of medication intended for administration that is meant for use in a single patient for a single case, procedure or injection.

[(X)](CC) Sterilization: A validated process used to render a *[product] preparation* free of viable organisms.

[(Y)](DD) Temperatures:

1. Frozen means temperatures between twenty-**five degrees** below zero and ten degrees

below zero Celsius (-~~20~~**25** and -10°C) (~~four~~**thirteen degrees** below zero and fourteen degrees Fahrenheit (-~~4~~**13** and 14°F)).

2. Refrigerated means temperatures between two and eight degrees Celsius (2 and 8°C) (thirty-six and forty-six degrees Fahrenheit (36 and 46°F)).
3. ~~Room temperatures means room temperatures between fifteen and thirty degrees Celsius (15 and 30°C) (fifty-nine and eighty-six degrees Fahrenheit (59 and 86°F)).~~ **Controlled room temperatures means a temperature maintained thermostatically that encompasses the usual and customary working environment 20° to 25° Celsius (68 to 78° F). Excursions between 15° and 30° Celsius (59 to 86° F) as commonly experienced in pharmacies and other facilities shall be deemed compliant.**

(EE) USP: The United States Pharmacopeia and the National Formulary (USP-NF) as adopted and published by the United States Pharmacopeial Convention, effective May 2013. Copies of the USP-NF are published by, and available from, USP, 12601 Twinbrook Parkway, Rockville, MD 20852-1790 or online at <http://www.usp.org/>. The USP-NF is incorporated herein by reference. This rule does not include any later amendments or additions to the USP-NF.

~~[(Z)]~~**(FF)** Validation: Documented evidence providing a high degree of assurance that specific processes will consistently produce a ~~[product]~~ **preparation** meeting predetermined specifications and quality attributes.

~~[(AA)]~~**(GG)** Definitions of sterile compounded ~~[products]~~ **preparations** by risk level:

1. Risk Level 1: Applies to compounded sterile ~~[products]~~ **preparations** that exhibit characteristics A., B., ~~[and]~~ **or** C., stated below. All Risk Level 1 ~~[products]~~ **preparations** shall be prepared with sterile equipment~~,~~ **and** sterile ingredients and solutions ~~[and sterile contact surfaces for the final product]~~ **in an ISO Class 5 environment**. Risk Level 1 includes the following:
 - A. ~~[Products]~~ **Preparations**:
 - (I) Stored at **controlled** room temperature and ~~[completely administered within]~~ **assigned a beyond-use date of** forty-eight (48) hours ~~[after preparation]~~ **or less**; or
 - (II) Stored under refrigeration ~~[for]~~ **and assigned a beyond-use date of** seven (7) days or less ~~[before complete administration to a patient over a period not to exceed forty-eight (48) hours];~~ or
 - (III) ~~[Frozen for thirty (30) days or less before complete administration to a patient over a period not to exceed forty-eight (48) hours.]~~ **Stored frozen and assigned a beyond-use date of thirty (30) days or less.**
 - B. Unpreserved sterile ~~[products]~~ **preparations** prepared for administration to one (1) patient or batch-prepared ~~[products]~~ **preparations** containing suitable preservatives prepared for administration to more than one (1) patient **with an assigned beyond-use date that does not exceed the beyond-use date allowed under section (1)(GG)1.A. of this rule.**
 - C. ~~[Products]~~ **Preparations** prepared by closed-system aseptic transfer of sterile, nonpyrogenic, finished pharmaceuticals (e.g., from vials or ampules) obtained from licensed manufacturers into sterile final containers obtained from licensed

manufacturers **with an assigned beyond-use date that does not exceed the beyond-use date allowed under section (1)(GG)1.A. of this rule.**

2. Risk Level 2: Sterile **[products] preparations** exhibit characteristic A., B., or C., stated below. All Risk Level 2 **[products] preparations** shall be prepared with sterile equipment~~[,]~~ **and** sterile ingredients **[and solutions and sterile contact surfaces for the final product] in an ISO Class 5 environment** and with closed-system transfer methods. Risk Level 2 includes the following:
 - A. **[Products stored beyond seven (7) days under refrigeration, stored beyond thirty (30) days frozen or administered beyond forty-eight (48) hours after preparation and storage at room temperature.] Preparations stored under refrigeration and assigned a beyond-use date greater than seven (7) days or preparations stored frozen and assigned a beyond-use date greater than thirty (30) days or preparations stored at controlled room temperature and assigned a beyond-use date greater than forty-eight (48) hours.**
 - B. Batch-prepared **[products] preparations** without preservatives that are intended for use by more than one (1) patient.
 - C. **[Products] Preparations** compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from a licensed manufacturer by using closed-system aseptic transfer (e.g., automated compounder).
3. Risk Level 3: Sterile **[products] preparations** exhibit either characteristic A. or B.:
 - A. **[Products] Preparations** compounded from nonsterile ingredients or compounded with nonsterile components, containers or equipment before terminal sterilization.
 - B. **[Products] Preparations** prepared by combining multiple ingredients (sterile or nonsterile) by using an open-system transfer or open reservoir before terminal sterilization.

(2) Policy and Procedure Manual/Reference Manuals.

- (A) A manual, outlining policies and procedures encompassing all aspects of Risk Level 1, 2 and 3 **[products] compounding**, shall be available for inspection at the pharmacy. The manual shall be reviewed on an annual basis. The pharmacy shall have current reference materials related to sterile **[products] preparations**.

(3) Personnel Education, Training and Evaluation.

- (A) Risk Level 1: All pharmacy personnel preparing sterile **[products] preparations** must receive suitable didactic and experiential training **in aseptic technique and procedures and shall be skilled and trained to accurately and competently perform the duties assigned. Additional training must be provided if the risk level of sterile activity conducted by the individual changes or if there is a change in compounding methods performed. To ensure competency, individuals preparing sterile preparations must successfully pass an Aseptic Technique Skill Assessment that complies with section (10) of this rule. The pharmacy shall establish policies and procedures for staff training and assessment.**

- (B) Risk Level 2: In addition to Risk Level 1 requirements, personnel training **must** include[s] assessment of competency in all Risk Level 2 procedures via process simulation.
- (C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, operators have specific education, training and experience to prepare Risk Level 3 **[products] preparations**. The pharmacist knows principles of good compounding practice for risk level **[products] preparations**, including—
1. Aseptic processing;
 2. Quality assurance of environmental, component, and **[end-product] end-preparation** testing;
 3. Sterilization; and
 4. Selection and use of containers, equipment, and closures.
- (4) Storage and Handling in the Pharmacy.
- (A) Risk Level 1 and 2: Solutions, drugs, supplies and **compounding** equipment must be stored **[according to manufacturer or USP requirements] and maintained in a manner that will maintain the chemical and microbiological stability of CSPs**. Refrigeration **[and]**, freezer **and, if applicable, incubator** temperatures shall be documented daily. Other storage areas shall be inspected regularly to ensure that temperature and lighting meet requirements. Drugs and supplies shall be shelved above the floor. Removal of **[products] drugs and supplies** from boxes shall be done outside **the** controlled **and buffer** areas. Removal of used supplies from the controlled area shall be done at least daily. **[Product] Preparation** recall procedures must **comply with section (21) of this rule and must** permit retrieving affected **[products] preparations** from specific involved patients.
- (B) Risk Level 3: In addition to Risk Level 1 and 2 requirements, **the pharmacy must establish** procedures **[include] for** procurement, identification, storage, handling, testing, and recall of components and finished **[products] preparations**. Finished **[but untested]** Risk Level 3 **[products] preparations awaiting test results** must be quarantined under minimal risk for contamination **in a manner that will maintain chemical and microbiological stability**.

[(5) Facilities and Equipment.

- (A) Risk Level 1: *The controlled area shall be separated from other operations. The controlled area must be clean and well lit. A sink with hot and cold water must be near, but not in, the controlled area. The controlled area and inside equipment must be cleaned and disinfected regularly. Sterile products must be prepared in at least a Class 100 environment (the critical area). Computer entry, order processing, label generation, and record keeping shall be performed outside the critical area. The critical area must be disinfected prior to use. A workbench shall be recertified every six (6) months and when it is moved; prefilters must be visually inspected on a regularly scheduled basis and replaced according to manufacturer's specifications. Pumps utilized in the compounding process shall be recalibrated and documented according to manufacturer procedures.*
- (B) Risk Level 2: *In addition to all Risk Level 1 requirements, the controlled area*

must meet Class 10,000 clean room standards; cleaning supplies should be selected to meet clean room standards; critical area work surface must be cleaned between batches; floors should be disinfected daily; equipment surfaces weekly; and walls monthly; with applicable environmental monitoring of air and surfaces. Automated compounding devices must be calibrated and verified as to accuracy, according to manufacturer procedures. Clean rooms not utilized on a daily basis must be cleaned prior to use as stated above.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, products must be prepared in a Class 100 workbench in a Class 10,000 clean room, in a Class 100 clean room or within a positive pressure barrier isolator. Access to the clean room must be limited to those preparing the products and who are in appropriate garb. Equipment must be cleaned, prepared, sterilized, calibrated, and documented according to manufacturer's standards. Walls and ceilings must be disinfected weekly. All non-sterile equipment that is to come in contact with the sterilized final product must be sterilized before introduction in the clean room. Appropriate cleaning and disinfection of the environment and equipment are required.]

(5) Facilities and Equipment. The pharmacy shall establish and follow proper controls to ensure environmental quality, prevent environmental contamination, and maintain air quality in all ISO classified areas.

(A) Risk Level 1: Risk Level 1 preparations must be prepared in a PEC located in a controlled area that meets the requirements of this rule. A sink with hot and cold water must be near, but not in, the controlled area. The controlled area and inside equipment must be cleaned and disinfected as provided in section (17) of this rule. Activities within the critical area shall be kept to a minimum to maintain the ISO classified environment. Primary engineering controls shall meet the requirements of section (6) of this rule; prefilters must be visually inspected on a regularly scheduled basis and replaced according to manufacturer's specifications. Pumps utilized in the compounding process shall be recalibrated and documented according to manufacturer procedures.

(B) Risk Level 2: In addition to all Risk Level 1 requirements, Risk Level 2 preparations must be prepared in a PEC located in a buffer area or prepared in a RABS located within a controlled area. Applicable environmental monitoring of air and surfaces must be conducted. Risk Level 2 preparations shall at a minimum remain a Risk Level 2 for the life of the preparation.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, Risk Level 3 preparations must be prepared in a PEC located in a buffer area or prepared in a RABS located within a controlled area. All non-sterile equipment that is to come in contact with the sterilized final preparation must be sterilized before introduction in the buffer area or into the RABS. Once compounded, Risk Level 3 preparations shall at a minimum remain Risk Level 3 for the life of the preparation.

(D) Automated compounding devices shall be tested for content, volume, and weight accuracy prior to both initial and daily use according to manufacturer procedures.

Test results shall be reviewed by a pharmacist to ensure compliance. The identity of the reviewing pharmacist and the review date shall be documented in the pharmacy's records.

- (E) All PECs and ISO classified areas shall be certified to ensure compliance with the requirements of this rule prior to beginning sterile compounding activities and every six (6) months thereafter. Certification shall be conducted by competent staff/vendors using recognized and appropriate certification and testing equipment. Certification results shall be reviewed by a pharmacist once received. Deficiencies or failures shall be investigated and corrected prior to further compounding which may include recertification of the PEC/ISO classified area.

1. The PEC and ISO classified areas must be recertified when: (1) any changes or major service occurs that may affect airflow or environmental conditions or (2) the PEC or room is relocated or the physical structure of the ISO classified area has been altered.
2. Corrections may include, but are not limited to, changes in the use of the affected PEC or ISO classified area or initiating a recall. The identity of the pharmacist conducting the required review and the review date shall be documented in the pharmacy's records.

- (F) Pressure Differential: If the controlled area is equipped with a device to monitor pressure differential, pressure differential results must be recorded and documented each day that the pharmacy is open for pharmacy activities. Alternatively, a continuous monitoring system may be used to record pressure differential results if the system maintains ongoing documentation of pressure recordings or maintains pressure alerts that are reviewed daily.

[(6) Apparel.

- (A) Risk Level 2: *In the controlled area, personnel wear low particulate, clean clothing covers. Head and facial hair is covered. Gloves, gowns, and masks are required. During sterile preparation gloves shall be rinsed frequently with a suitable agent and changed when integrity is compromised.*
- (B) Risk Level 3: *In addition to Risk Level 2 requirements, clean room apparel must be worn inside the controlled area at all times during the preparation of Risk Level 3 sterile products except when positive pressure barrier isolation is utilized. Attire shall consist of a low-shedding coverall, head cover, face mask, and shoe covers.]*

(6) Primary Engineering Controls (PECs):

- (A) PECs must be properly used, operated, and maintained and must be located out of traffic patterns and away from conditions that could adversely affect their operation or disrupt intended airflow patterns (e.g., ventilation systems or cross-drafts).
- (B) PECs shall maintain ISO Class 5 or better conditions during dynamic operating conditions and while compounding sterile preparations, including, when transferring ingredients into and out of the PEC and during exposure of critical sites;

- (C) PECs shall provide unidirectional (laminar flow) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites.
 - (D) The recovery time to achieve ISO Class 5 air quality in any PEC shall be identified in the pharmacy's policies and procedures. Procedures must be developed to ensure adequate recovery time is allowed before or during compounding operations and after material transfer.
- (7) **Controlled Areas.** The controlled area shall be designed, maintained and controlled to allow effective cleaning and disinfection and to minimize the risk of contamination and the introduction, generation, and retention of particles inside the PEC.
- (A) Controlled areas must be clean and well-lit and shall be free of infestation by insects, rodents, and other vermin. Trash shall be disposed of in a timely and sanitary manner and at least daily. Tacky mats or similar articles are prohibited in the controlled area or any ISO classified environment.
 - (B) Traffic flow in or around the controlled area shall be minimized and controlled. Food items, chewing gum, eating, drinking, and smoking are prohibited in the area;
 - (C) Nonessential objects that shed particles shall not be brought into the controlled area, including, but not limited to, pencils, cardboard cartons, paper towels, and cotton items (e.g., gauze pads). Furniture, carts, supplies, and equipment shall be removed from shipping cartons/containers and properly cleaned and disinfected with sterile alcohol before entering any ISO classified area. No shipping or other external cartons may be taken into the controlled area or an ISO classified area.
 - (D) Only supplies essential for compounding shall be stored in the controlled area. Supplies or other non-essential equipment shall not be stored in or on the PEC.
- (8) **Garbing and Hand Hygiene.** Individuals engaged in, or assisting with, CSPs shall be trained and demonstrate competence in proper personal garbing, gloving, and hand hygiene. Competence must be documented and assessed through direct visual observation as part of the aseptic technique skill assessment required by this rule.
- (A) **Risk Level 1:** Low-particulate and non-shedding gowns, hair covers, gloves, face masks, and beard covers must be worn during compounding and cleaning. All head and facial hair must be covered. During sterile preparation, gloves shall be disinfected before use and frequently thereafter with a suitable agent and changed when integrity is compromised. All personnel in the controlled area must be appropriately garbed as required by this section.
 - (B) **Risk Level 2 and Risk Level 3:** In addition to Risk Level 1 requirements, shoe covers and sterile gloves must be worn while compounding and cleaning, including, over RABS gloves. All personnel in the controlled or buffer area must garb as required by this section.
- [(7)](9) **Aseptic Technique and [Product] Preparation.** Appropriate quality control methods shall be maintained over compounding methods at all times to ensure proper aseptic technique.
- (A) **Risk Level 1:** Sterile [products] preparations must be prepared in [a Class 100] an **ISO Class 5** environment. Personnel shall scrub their hands and forearms [for an

appropriate period at the beginning of each aseptic compounding process] a minimum of thirty (30) seconds and remove debris from underneath fingernails under warm running water before donning the required gloves. Eating, drinking and smoking are prohibited in the controlled area. Talking shall be minimized to reduce airborne particles. Ingredients shall be determined to be stable, compatible, and appropriate for the *[product] preparation* to be prepared, according to manufacturer, USP, or scientific references. Ingredients and containers shall be inspected for defects, expiration and integrity before use. Only materials essential for aseptic compounding shall be placed in the *[workbench] PEC. [Surfaces of ampules and vials shall be disinfected before placement in the workbench.] Supplies, equipment, and the surfaces of ampules and vials shall be disinfected before entering the PEC by wiping the outer surface with sterile alcohol or an equivalently effective non-residue generating disinfectant.* Sterile components shall be arranged in the *[workbench] PEC* to allow **a clear, uninterrupted [laminar airflow] path of HEPA-filtered air** over critical *[surfaces of needles, vials, ampules, etc] sites*. Automated devices and equipment shall be cleaned, disinfected and placed in the *[workbench] PEC* to enable laminar airflow. Aseptic technique shall be used to avoid touch contamination of critical sites of containers and ingredients. Particles shall be filtered from solutions, **if applicable**. Needle cores shall be avoided. The pharmacist shall check before, during, and after preparation to verify the identity and amount of ingredients before release.

- (B) Risk Level 2: In addition to Risk Level 1 requirements, a file containing **the** formula, components, procedures, sample label, and final evaluation shall be made for each *[product] preparation* batch. A separate work sheet and lot number for each batch shall be completed. When combining multiple sterile *[products] preparations*, a second verification of calculations shall take place. The pharmacist shall verify data entered into any automatic compounder before processing and check the end *[product] preparation* for accuracy.
- (C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, nonsterile components must meet **compendial** standards *[if available, as] or must be* verified by a pharmacist and a certificate of analysis. Batch preparation files shall also include comparisons of actual with anticipated yields, sterilization methods, and quarantine specifications. Presterilized containers shall be used when feasible. Final containers must be sterile and capable of maintaining *[product] preparation* integrity throughout the shelf life. Sterilization methods must be based on properties of the *[product] preparation and must be conducted in a method recognized for the preparation and confirmed through sterility testing according to USP requirements.*
- (D) **Single-dose vials/containers and pharmacy bulk vial/containers exposed to ISO Class 5 or cleaner air may be used in compounding until the assigned in-use time which shall not exceed six (6) hours after initial needle puncture, unless otherwise specified by the manufacturer. Opened single-dose ampules shall not be stored for any time period. The in-use time must be placed on the vial/container.**
- (E) **Unless otherwise specified by the manufacturer, multiple-dose vials/containers with an antimicrobial preservative may be used in compounding until the assigned in-use date which shall not exceed twenty-eight (28) days after initially entering or opening**

the vial/container (e.g., needle-puncture). The in-use date must be placed on the vial/container.

[(8) Process Validation.

- (A) Risk Level 1:** All pharmacy personnel who prepare sterile products shall pass a process validation of aseptic technique before compounding sterile products. Pharmacy personnel competency must be reevaluated by process validation at least annually, whenever the quality assurance program yields an unacceptable result, or whenever unacceptable techniques are observed. If microbial growth is detected, the entire sterile process must be evaluated, corrective action taken, and the process simulation test performed again.
- (B) Risk Level 2:** In addition to Risk Level 1 requirements, process simulation procedures shall cover all types of manipulations, products and batch sizes.
- (C) Risk Level 3:** In addition to all Risk Level 1 and 2 requirements, written policies shall be maintained to validate all processes, procedures, components, equipment and techniques.]

(10) Aseptic Technique Skill Assessment. Individuals engaged in sterile compounding must take and successfully pass an aseptic technique skill assessment to verify aseptic competency. The assessment must include a direct visual observation of the individual's aseptic competency during a process simulation that represents the most challenging or stressful conditions encountered or performed by the person being evaluated. The assessment must include media fill testing for all risk levels.

(A) The required visual observation shall assess:

- 1. Proper aseptic technique, manipulations and work practices, including, but not limited to, avoiding touch contamination, proper use of first air and if applicable, sterilizing high risk CSPs;**
- 2. Cleaning and disinfection;**
- 3. Hand hygiene, gloving, and garbing;**
- 4. Identifying, weighing, and measuring of ingredients;**
- 5. Maintaining sterility in ISO Class 5 areas;**
- 6. Labeling and inspecting CSPs for quality.**

(B) Media-Fill Testing. Pharmacies shall establish and follow policies and procedures for media-fill testing. Media-fill testing shall comply with USP Chapter 797's recommended procedures and methods and must be conducted using the most challenging or stressful conditions/compounding actually encountered or performed by the person being evaluated using the same container or closure. A minimum of three (3) media-fill tests must be completed during initial media-fill testing and one (1) media-fill test completed for ongoing testing.

(C) Frequency: The required Aseptic Technique Skill Assessment must be conducted prior to initial compounding and every twelve (12) months thereafter for Risk Levels 1 and 2 compounding and every (6) months thereafter for Risk Level 3 compounding. Additionally, an Aseptic Technique Skill Assessment must be conducted whenever the quality assurance program yields an unacceptable result, whenever unacceptable

techniques are observed, if the risk level of sterile activity conducted by the individual changes or if there is a change in compounding methods performed.

- (D) Individuals who fail written tests; visual observation of hand hygiene, garbing, or aseptic technique; or media-fill tests must undergo immediate requalification through additional training by competent compounding personnel. Individuals who fail visual observation of hand hygiene, garbing, or aseptic technique; or media-fill tests must pass three (3) successive reevaluations in the deficient area before they can resume compounding of sterile preparations.

[(9)(11) Record Keeping.

(A) Risk Level 1: The following must be documented:

1. Training and competency evaluation of pharmacy personnel involved in sterile **[product preparation] compounding, including, the dates and results of the required aseptic technique training, aseptic technique skill assessment and media-fill testing;**
2. Refrigerator, **[and] freezer and, if applicable, incubator** temperature logs;
3. Certification **[of workbenches] dates and results for any PEC or ISO classified area;**
4. **[Copies of any m]Manufacturer [standards] manuals** that are relied upon to maintain compliance with this rule; **[and]**
5. Other facility quality control logs as appropriate including all maintenance, cleaning, and calibration records**[.]; and**
6. **If applicable, pressure recordings including documentation of the review of continuous monitoring system results as required by section (5)(F).**

(B) Risk Level 2: In addition to Risk Level 1 requirements, records of any **[end-product] end-preparation** testing and batch preparation records must be maintained.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, record requirements for Risk Level 3 **[products] preparations** must include:

1. Preparation work sheet;
2. Sterilization records;
3. Quarantine records, if applicable;
4. **[End-product] End-preparation** evaluation and testing records as required in section **[(12)(14)]**; and
5. Ingredient validation records as required in section **[(12)(14)]**.

(D) All records and reports shall be maintained **either electronically or physically** for two (2) years and shall be readily retrievable**[,]and** subject to inspection**[s]** by the board of pharmacy or its agents. **At a minimum, records shall be physically or electronically produced immediately or within two (2) hours of a request from the board or the board's authorized designee.**

[(10)(12) Labeling.

Sterile **[products dispensed to patients] preparations** shall be labeled in accordance with section 338.059, RSMo and with the following supplemental information **[affixed to a permanent label]**:

1. Beyond-use date;
2. Storage requirements **if stored at other than controlled room temperature**;
3. Any device specific instructions; *[and]*
4. Auxiliary labels, when applicable*[.]*; **and**

5. If applicable, a designation indicating the preparation is hazardous.

[(B) Risk Level 2: All requirements for Risk Level 1 must be met.

(C) Risk Level 3: All requirements for Risk Level 1 must be met.]

[(11)](13) Beyond-Use Dating.

- (A) Risk Level 1 **and Risk Level 2**: All sterile *[products] preparations* must bear a beyond-use date. Beyond-use dates *[are] must be* assigned based on current drug **and microbiological** stability information and sterility considerations.
- (B) *[Risk Level 2: All requirements for Risk Level 1 must be met.*
- (C)]* Risk Level 3: In addition to all Risk Level 1 requirements, there must be a reliable method for establishing all *[expiration] beyond-use* dates, including laboratory testing of *[product] preparation* stability, pyrogenicity, particulate contamination and potency. *[Expiration dating not specifically referenced in the product's approved labeling or not established by product specific instrumental analysis, shall be limited to thirty (30) days.]* Beyond-use dating not specifically referenced in the products approved labeling or not established by *[product] preparation* specific instrumental analysis shall be limited to thirty (30) days. There must be a reliable method for establishing all beyond-use dating. *[Products maintaining beyond-use dating] Preparations assigned a beyond-use date* of greater than thirty (30) days shall have lab testing of *[product] preparation* stability and potency.

[(12)](14) [End-product] End-preparation Evaluation.

- (A) Risk Level 1: The final *[product] preparation* must be inspected for **clarity**, container leaks, integrity*[,]* **and appropriate** solution cloudiness or phase separation, *[particulates in solution, appropriate]* solution color, and solution volume. The pharmacist must verify that the *[product] preparation* was compounded accurately as to the ingredients, quantities, containers, and reservoirs. Background light or other means for the visual inspection of *[products] preparations* for any particulate and/or foreign matter must be used as part of the inspection process, **provided an alternate means of inspection shall be used if a visual inspection or exposure to the preparation may pose a health hazard.**
- (C) Risk Level 3: In addition to all Risk Level 1 requirements, the process validation procedure shall be supplemented with a program of *[end-product] end-preparation* sterility testing according to a formal sampling plan. Samples shall be statistically valid to ensure that batches are sterile. A method for recalling batch *[products] preparations* shall be established if *[end-product] preparation* testing results are unacceptable. *[All sterile products] A sample from each sterile preparation/batch* must be tested for sterility. *[All parenteral sterile products] A sample from each parenteral sterile preparation/batch* must also be tested for pyrogenicity. *[Sterile products compounded from nonsterile components] Risk Level 3 preparations* must be

quarantined **and stored to maintain chemical and microbiological stability** pending results of **[end-product] end-preparation** testing.

1. Sterility testing: Sampling for the sterility test shall occur promptly upon the completion of preparation. The sterility test, including the sampling scheme, shall be conducted according to **[one (1) of the USP methods] a method recognized for the preparation by USP Chapter 71.**
 2. Pyrogen/Endotoxin testing: **[Each s]Sterile parenteral [product] preparations** prepared from non-sterile drug components shall be tested for pyrogen or endotoxin according to **[recommended USP methods] a method recognized by USP Chapter 151 for pyrogen testing and recognized by USP Chapter 85 for endotoxin testing.**
 3. Potency: The pharmacy shall have a procedure for a pre-release check of the potency of the active ingredients in the compounded sterile **[product] preparation** prepared from non-sterile bulk active ingredients. The procedure shall include at least the following verifications by a pharmacist:
 - A. The lot of the active ingredients used for compounding have the necessary labeling, potency, purity, certificate of analysis and other relevant qualities;
 - B. All weighings, volumetric measurements, and additions of ingredients were carried out properly;
 - C. The compounding or control records include documentation that the fill volumes of all units available for release were checked and were correct; and
 - D. The final potency is confirmed by instrumental analysis for sterile **[products] preparations** that have been assigned a beyond-use date of more than thirty (30) days.
- (D) Emergency Dispensing of a Risk Level 3 Sterile **[Product] Preparation**: When a compounded Risk Level 3 **[product] preparation** must be released prior to the completion of testing, the sterile **[product] preparation** may be dispensed pending test results. **Emergency dispensing shall be defined as, and comply with, section (1)(N) of this rule.**

~~[(13)](15) [Handling Sterile Products Outside the Pharmacy] Storage, Handling, and Transport.~~

- ~~[(A) Risk Level 1:] Sterile preparations shall be packaged, stored, dispensed, and distributed in a manner that will maintain the preparation's chemical and microbiological stability until the assigned beyond-use date or until delivery to the patient or intended recipient.~~** The pharmacist-in-charge shall assure the environmental control of all sterile compounded **[products] preparations** shipped. Sterile **[products] preparations** shall be transported so as to be protected from excesses of temperatures and light within appropriate packaging or delivery containers that maintain necessary storage conditions to preserve the quality and integrity of sterile **[products] preparations**. The pharmacy shall follow written procedures that specify packing techniques, configuration, and materials for groups of **[products] preparations** with common storage characteristics and for specific **[products] preparations** where unique storage conditions are required to retain adequate stability and **[product] preparation**

quality.

[(B) Risk Level 2: All requirements for Risk Level 1 must be met.

(C) Risk Level 3: All requirements for Risk Level 1 must be met.]

(16) Point-of-Care Assembled Systems. Assembly of point-of-care assembled systems shall be considered Risk Level 1 compounding. Point-of-care assembled systems shall be assigned a beyond-use date which may exceed the beyond-use-date authorized for Risk Level 1 preparations provided the date is assigned in accordance with the manufacturer's recommendations or labeling.

(A) When dispensed, an assembled non-activated system shall be labeled with beyond-use dates for both activated and non-activated states. The compounding record must document both dates. The beyond-use date of an assembled non-activated system shall be limited to a maximum of fifteen (15) days unless the pharmacy has documentation from the system's manufacturer that a longer date is acceptable.

(B) Point of care assembled systems shall be assembled and stored in accordance with the manufacturer's labeling and recommendations.

(17) General Cleaning and Disinfection Requirements. Except as otherwise provided herein, cleaning and disinfection of controlled and buffer areas, supplies and equipment shall be performed and conducted in accordance with USP Chapter 797 timeframes and procedures. Controlled areas that do not meet ISO air classifications shall be cleaned and disinfected as required by USP Chapter 797 for segregated compounding areas. If compounding is done less frequently than the cleaning and disinfection timeframes specified in USP Chapter 797, cleaning and disinfection must occur before each compounding session begins.

(A) The pharmacy shall establish and follow written policies and procedures governing all aspects of cleaning and disinfection, including, approved cleaning/disinfecting agents and materials, schedules of use, and methods of application.

(B) Individuals shall be trained in proper cleaning and disinfection procedures prior to performing such activities. Training shall include direct visual observation of the individual's cleaning and disinfecting process by qualified staff. The individual shall be annually reassessed for competency through direct visual observation. Documentation of the required training and training dates shall be maintained in the pharmacy's records. Individuals who fail to demonstrate competency shall be reinstructed and successfully reevaluated prior to any further cleaning or disinfection.

(C) Cleaning and disinfection activities shall be performed using approved cleaning/disinfection agents and procedures described in the pharmacy's written policies and procedures. Manufacturers' directions for minimum contact time shall be followed.

(D) All cleaning tools (e.g., wipes, sponges, and mop heads) must be low-lint and dedicated for use in the controlled area and buffer area.

(E) Primary engineering controls shall be cleaned with a germicidal agent followed by sterile alcohol. Sterile water for irrigation shall be used to dilute germicidal agents

used inside the PEC that require dilution.

(F) At a minimum, the critical area shall be cleaned and disinfected prior to compounding, between batches, and whenever contamination is suspected using sterile alcohol which is allowed to dry immediately prior to compounding.

(18) Environmental Sampling/Testing. The pharmacy shall establish and follow proper controls to ensure environmental quality, prevent environmental contamination, and maintain air quality in all ISO classified areas. Applicable environmental monitoring of air and surfaces must be conducted. Air monitoring must be conducted prior to initial compounding and every six (6) months thereafter. Surface sampling/monitoring must be conducted every six (6) months for Risk Level 2 and every thirty (30) days for Risk Level 3 compounding.

~~[(14)]~~**(19) Cytotoxic Drugs.**

(A) The following additional requirements are necessary for those licensed pharmacies that prepare cytotoxic drugs to insure the protection of the personnel involved:

1. Cytotoxic drugs shall be compounded in a vertical flow, Class II biological safety cabinet or *[an isolator]* **a CACI**. If used for other *[products]* **preparations**, the cabinet must be thoroughly cleaned;
2. Protective apparel shall be worn by personnel compounding cytotoxic drugs which shall include disposable masks, gloves and gowns with tight cuffs;
3. Appropriate safety and containment techniques for compounding cytotoxic drugs shall be used in conjunction with the aseptic techniques required for preparing sterile *[products]* **preparations. Chemotherapy preparations should be compounded using a closed system transfer device;**
4. Appropriate disposal containers for used needles, syringes, and if applicable, cytotoxic waste from the preparation of chemotherapy agents and infectious waste from patients' homes. Disposal of cytotoxic waste shall comply with all applicable local, state and federal requirements;
5. Written procedures for handling major and minor spills and generated waste of cytotoxic agents must be developed and must be included in the policy and procedure manual;
6. Prepared doses of cytotoxic drugs must be labeled with proper precautions inside and outside, and shipped in a manner to minimize the risk of accidental rupture of the primary container.

[(15) Exemption: Pharmacists and pharmacies where sterile compounding is provided may be exempt from this rule when compounding is restricted to utilizing compounds or products that are contained only in a closed or sealed system and can be transferred or compounded within this self-contained system or topical products that require further transfer or combination in order to achieve a finished product without further modification of the product.]

[(16) In addition to the requirements outlined in this rule, all standards and requirements

as outlined in 20 CSR 2220-2.400 must be maintained. Pharmacies that are registered with the Food and Drug Administration (FDA) are exempt from the distribution restrictions in 20 CSR 2220-2.400(12) for compounded sterile pharmaceuticals distributed with FDA's knowledge and enforcement discretion. This exemption applies only to a twenty-four (24)-hour course of therapy which is needed:

(A) To treat an emergency situation; or

(B) For an unanticipated procedure for which a time delay would negatively affect a patient outcome. In order to continue beyond twenty-four (24) hours, the pharmacy must obtain a prescription and comply with all record and labeling requirements as defined by law or regulation.]

(20) Remedial Investigations: A remedial investigation shall be required if: (1) any sampling or testing required by this rule demonstrates a colony forming unit (CFU) count that exceeds USP Chapter 797 recommended action levels for the type of sampling/testing or (2) if a highly pathogenic microorganism is detected in any preparation or ISO classified area (e.g., Gram-negative rods, coagulase positive staphylococcus, molds, fungus or yeasts).

(A) CSPs and any ingredients used within the compounding process that are part of the remedial investigation shall be quarantined until the results of the investigation are known. All affected areas shall be resampled to ensure a suitable state of microbial control prior to further compounding. The pharmacy shall ensure that no misbranded, contaminated, or adulterated CSP is administered or dispensed for patient use.

(B) The pharmacy shall notify the board in writing within seven (7) days if any preparation or environmental monitoring/testing detects a highly pathogenic microorganism, regardless of CFU count.

(21) Recalls. A recall must be initiated when a CSP is deemed to be misbranded, adulterated, or non-sterile or if end-preparation testing results are out of specification. The pharmacy shall notify the prescriber of the nature of the recall, the problem(s) identified and any recommended actions to ensure public health and safety. In cases where the CSP has the potential to harm the patient, the same notification shall be provided to all patients that received the recalled CSP(s). Any recall initiated by a pharmacy shall be reported, in writing, to the board within three (3) business days. The pharmacy shall document their activities related to the recall.

*AUTHORITY: sections 338.140, 338.240, **RSMo 2013**, [and] **section** 338.280, RSMo 2000 and section 338.010, RSMo Supp. [2007] 2014. This rule originally filed as 4 CSR 220-2.200. Original rule filed May 4, 1992, effective Feb. 26, 1993. Amended: Filed Oct. 28, 1994, effective May 28, 1995. Rescinded and readopted: Filed Dec. 3, 2002, effective July 30, 2003. For intervening history, please consult the Code of State Regulations. Amended: Filed July 25, 2016.*

PUBLIC COST: This proposed rule will not cost state agencies or political subdivisions more than five hundred dollars (\$500) in the aggregate.

PRIVATE COST: This proposed amendment will cost private entities ninety-nine thousand, two hundred forty-five dollars (\$99,245) during the first year of implementation, two million eight hundred sixty-one thousand two hundred fifty-nine dollars and thirty-five cents (\$2,861,259.35) annually of the life of the rule as the result of the proposed amendment.

NOTICE TO SUBMIT COMMENTS: Anyone may file a statement in support of or in opposition to this proposed amendment with the Missouri Board of Pharmacy, PO Box 625, 3605 Missouri Boulevard, Jefferson City, MO 65102, by facsimile at (573) 526-3464, or via email at pharmacy@pr.mo.gov. To be considered, comments must be received within thirty (30) days after publication of this rule in the Missouri Register. No public hearing is scheduled.